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Editorial: Newer initiatives in detection, drug discovery and therapeutic management of drug-resistant tuberculosis

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Editorial on the Research Topic
Newer initiatives in detection, drug discovery and therapeutic management of drug-resistant tuberculosis

In 2023, 10.8 million people fell ill with tuberculosis (TB) with an estimated 1.25 million deaths globally. While 400,000 people were diagnosed with multi-drug resistant (MDR) and/or rifampicin-resistant (RR) TB, only 175, 923 of them were started on treatment. Poor treatment coverage is primarily due to cost, poor clinical practice, lack of awareness and drug resistance. Although rapid molecular tests are endorsed by the World Health Organization (WHO) and recommended as an initial diagnostic screening tool, only 48% of the cases were diagnosed using these tools. The WHO's diagnostic pipeline has extended with a variety of tests, including near-point-of-care tests. There are 15 vaccine candidates and 29 drug candidates in various phases of TB clinical trials until August 2024. Besides, newer drug regimens and implementation studies are under evaluation for the potential to be better TB treatment options (1). Newer Initiatives in the detection, and therapeutic management of drug-sensitive, MDR/RR-TB are the need of the hour for efficient management of the global TB crisis. This was the focus of our Research Topic, which has five articles, including three research articles, a review, and a brief research report.

TB is a leading cause of death in humans due to a single infectious agent, namely *Mycobacterium tuberculosis* (Mtb). The initial infection is caused by inhaling aerosol droplets containing Mtb, which may progress to active TB disease in about 5% of infected individuals while ensuing as asymptomatic latent infection (LTBI) in the majority of the individuals. However, LTBI cases can reactivate to symptomatic TB when host immune system is suppressed. TB diagnosis is usually made by clinical, radiological, microbiological, and molecular testing of suspected individuals. Co-existence of TB with other conditions such as diabetes mellitus, hypertension, dyslipidemia and HIV poses an additional risk factor for the worsening of the TB disease (2). Though lungs are the primary organs involved in pulmonary

TB, the predominant form of TB, the disease can also affect various organ systems like the nervous, digestive, cutaneous, gastrointestinal, urogenital, skeletal, lymphatic, and cardiac systems as primary and/or disseminated disease, resulting in extrapulmonary TB (EP-TB). Diagnosis of EP-TB is more difficult than pulmonary TB while treatment is predominantly similar although adjuvant therapy may be required in some EP-TB cases (3). Drug resistance (DR) poses additional challenges in the diagnosis and treatment of cases than drug-sensitive TB. Although treatment of DR-TB includes different regimens with multiple drugs administered for several months, there is a significant need for newer drugs to treat DR-TB cases. A new drug discovery pipeline requires extensive research and screening of drugs with models and assays that would mimic the pathophysiological states of the bacilli in the lungs. Translation of the *in vitro* models into animal models and testing the clinical efficacy in actively dividing and persistent populations are additional stages in the drug development process (4). Nonetheless, the treatment regimen for DR-TB has reduced significantly, from > 1 year to 6 – 9 months by the inclusion of Bedaquiline, as shown in various clinical trials including the recently approved 6-month BPaLM regimen for MDR/RR-TB patients (5). However, due to the toxicity of drugs and prolonged treatment regimen, a personalized treatment approach can help to improve treatment outcomes in DR-TB (6).

There has been progress in recent years in the identification of drug targets and screening of bioactive compounds for use in TB therapy. In the review by Zhang et al., the authors discuss the current status of anti-TB drugs and the need for newer drug targets to alleviate the pathophysiology of TB. Among the potential targets for drug development, Mtb cell wall synthesis inhibitors targeting DprE (decaprenylphosphoryl-D-ribose 2-epimerase), MmpL3 (Mycobacterial membrane protein large 3), L-rhamnose synthesis-related enzymes, Enenyl-carrier protein reductase, and D-alanine-D-alanine ligase-A were discussed. Inhibitors for DprE and MmpL3 are in phase II clinical trials and offer promise as anti-TB drugs. In addition to fluoroquinolones, other DNA gyrase-binding novel compounds are currently assessed as anti-TB drugs. Inhibitors of thymidylate kinase, a DNA-binding enzyme with low similarity to human protein, are under evaluation as a TB drug target. Besides, bacterial enzymes involved in energy metabolism like ATP synthase and cytochromes as well as iron metabolism like siderophores are currently evaluated as potential drug targets to develop TB drugs.

Although various drugs are currently available, aminoglycosides like streptomycin and amikacin/kanamycin are used as first and second-line drugs for TB therapy. These drugs are injectables and are less preferred than other oral drugs. Apramycin is a drug approved in veterinary medicine with broad-spectrum microbicidal activity. It has a bicyclic sugar moiety and a mono-substituted deoxystreptamine in comparison to existing aminoglycosides like amikacin, which are bi-substituted deoxystreptamine. The study by Kaur et al. describes how apramycin has a unique octadiose core that makes it work against aminoglycoside resistance mechanisms in mycobacteria. Comparison of apramycin killing kinetics over 14 days showed strong bactericidal effects *in vitro* with Emax of 5.2 log10 CFU/ml compared to amikacin at 5.28 log10 CFU/ml. The intracellular efficacy of apramycin in human THP-1 macrophage cell lines over a 7-day period showed an Emax of 1.15 log10 CFU/ml reduction while amikacin typically did not show any reduction. Further, apramycin showed a better CFU/ml reduction compared to amikacin and moxifloxacin in Mtb biofilm. Importantly, apramycin showed an additive effect when combined with first-line anti-TB drugs in a mouse infection model and did not show any cytotoxicity to mammalian cell lines like THP-1, A549, and HepG2, offering a promising target for consideration to TB therapy. Interestingly, apramycin works against DR-TB strains with resistance to classical aminoglycosides like amikacin and kanamycin; thus increasing its therapeutic range for DR-TB.

Another anti-TB drug currently in use is p-amino salicylic acid (PAS), which is a pro-drug with a property to inhibit the dihydrofolate reductase of Mtb. Screening for antifolates is required with the emergence of DR-TB. Antifolates are typically designed to target Mtb *folK* and *folB*, which codes for dihydropteroate synthase and dihydrofolate reductase. In this Research Topic, Falcão et al. screened antifolates using purified Mtb FolB, which has aldolase/epimerase activity and is required for bacterial growth. A library of nearly 6,000 compounds was screened in an enzymatic assay using a microtiter 384-well plate. The authors designed the assay based on the fluorescence of 6-hydroxymethyl-7,8-dihydropterin (HP), the kinetic product formed by the action of Mtb FolB on the substrate 7,8-dihydroneopterin (DHNP). The hit compounds had a 30% reduction in fluorescence and a total of 19 hit compounds were studied by dose-response curve. The molecules were grouped into 5 independent clusters (numbered I-V), of which two of the cluster II and III molecules were confirmed to be active after resynthesis. All these compounds were tested in enzyme assays, molecular docking studies, and Mtb growth inhibition assays. The cluster II compounds comprised of the pyrazol-3-one series had an IC50 value of 18-47 μM, while the cluster III molecules, comprised of the sulfonamide series had an IC50 value of 2.6-15.4 μM. The docking studies highlighted two modes of binding for pyrazol-3-one compounds, while the sulfonamide series indicated several interactions with the catalytic Tyrosine-54 (Tyr54D) and Lysine99 (Lys99A) residues of Mtb FolB. One of these compounds showed modest inhibitory activity against Mb *in vitro*, offering promise as a new drug entity. Additional *in vivo* characterization and efficacy studies are warranted to elevate the status of these molecules as potential anti-TB drugs.

While diagnosis and treatment of pulmonary TB is complex and challenging, EP-TB, including its DR versions, is often misdiagnosed and/or inadequately diagnosed and treated. A study by Yu et al. describes the epidemiological characteristics of EP-TB patients from South Central China. In this study, retrospective data from culture-positive inpatients collected from January 2013 to December 2021 in a provincial institute and clinical center for TB in China was analyzed for EP-TB characteristics. Apart from the baseline characteristics of the DR profile, the drug-sensitivity test (DST) information was collected and drug-sensitive patients were excluded from the analysis. Of the 1,324 patients, there was a nearly equal distribution of EP-TB as well as EP-TB combined with pulmonary TB with a male-to-female sex ratio of 2.03 and a median age of 38 years. Overall, lymphatic TB was the most predominant form of EP-TB with 29.83% cases, while musculoskeletal (22.9%) and genitourinary (12.28%) showed exclusive EP-TB presentation without involvement of lungs.

Among the EP-TB cases, DR-TB was observed with resistance to RIF (12.39%), INH (20.85%), and MDR (11.18%) observed in patients. Trends in resistance among all 9 years showed INH resistance rates were the highest. The age group 40-49 showed the highest DR rates in EP-TB patients among all age groups. The study showed the highest INH resistance in musculoskeletal EP-TB, while single-drug resistance was predominant in TB meningitis. Multivariate analysis on age, gender, EP-TB type, occupation, and risk factors showed that DR was higher among the workers in the 40–49-year-old age group, those with musculoskeletal TB from the west of Hunan. Although the epidemiological analysis provided insights into DR-TB distribution among EP-TB patients, it would be interesting to look at additional factors like co-morbidities, treatment regimens, and outcomes in these patients to get insight into the development of DR-TB.

Comorbidities and associated infections play a key role in the prognosis of TB infection and treatment outcomes. Besides these, endemic infections like Schistosomiasis and strongyloidiasis are prominent among TB patients, contributing to the morbidity and mortality of these patients. In a multicentric retrospective study by Genovese et al., 228 patients (160 with TB infection and 68 with TB disease) with a median age of 46 years, attending a clinic in Italy with TB infection or disease were screened from June 2020 to January 2024 for Schistosomiasis and strongyloidiasis by serological tests including ELISA where there was a previous history. Patients positive for Schistosomiasis and strongyloidiasis by serological examination were then assessed by urine and stool examination. Baseline clinical and demographic data, including comorbidities and coinfections, were collected for statistical analysis. Screening of 53 patients for Schistosomiasis based on criteria like country of origin and previous history showed 12 positive cases. No significant differences in patient characteristics including the period of stay in Italy were observed between patients with positive and negative results for Schistosomiasis. Among the study group, the prevalence of strongyloidiasis was lower (7.8%) than Schistosomiasis (26.7%). The 12 patients positive for strongyloidiasis among 153 screened, showed no significant difference to strongyloidiasis-negative cases. Treatment of parasitic infections was done as standard practice and administration of praziquantel for Schistosomiasis was done following anti-TB treatment owing to the risk of cross-reactivity between rifampicin and praziquantel. The study highlights the importance of TB screening for parasitic infections beyond serology, in suspected cases, especially with migrant populations.

In summary, the Research Topic includes articles related to the treatment of DR-TB with insights into novel anti-TB drug targets, and the evaluation of drugs used in other therapeutic areas repurposed for TB. Inhibitors of folate metabolism, which was previously exploited for PAS, have been used to screen new compounds to enable the discovery of new and/or improved anti-TB drugs. In addition to pulmonary TB, DR profiling of EP-TB and its clinical characteristics are useful for understanding any possible risk factors in a population. Besides, the co-morbidity of TB with parasitic infections and associated metabolic derangement should be considered for effective TB management in endemic countries.

Author contributions

RG: Writing – original draft, Writing – review & editing. VA: Writing – original draft, Writing – review & editing. SN: Writing – original draft, Writing – review & editing. SS: Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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